Wyckoff et al., Academic Press (1985)). Therefore, the data can be used for optimizing an RRF inhibitor and more importantly, can be used for designing a novel RRF inhibitor and synthesizing it. The structure coordinate of RRF provided in the present invention facilitates the identification of related protein, enzyme or nucleic acid similar to RRF in function, structure or both of them. This enables more proper presumption of active site, binding site and so forth of RRF itself and the above-mentioned similar protein and the like, which leads to a novel antibacterial agents, herbicide or fungicide.

B1 cont

Please replace the paragraph beginning at line 18 of page 27 as shown. Applicants enclose a separate page indicating the amendments to the specification with deletions indicated by bracketing and additions indicated with underlining.

The following program is available from Oxford University, Oxford, UK: GPID (Goodford, P.J., "A Computational Procedure for Determining Energetically Favorable Binding Sites on Biologically Important Macromolecules", J. Med. Chem., 28, pp. 849-857 (1985)), and the following is available from Molecular Simulations, Burlington, MA: MCSS (Miranker, A or M. Karplus "Functionality Map of Binding Sites: A Multiple Copy Simultaneous Search Method.", Proteins: Structure, Function and Genetics, 11, pp. 29-34 (1991)). As for AUTODOCK (Goodsell, D.S. and A.J. Olsen, "Automated Docking of Substrates to Proteins by Simulated Annealing", Proteins: Structure, Function and Genetics, 8 pp. 195-202 (1990), it is available from Scripps Research Institute La Jolla, CA, and as for DOCK (Kuntz, I, D. et al, "A Geometric Approach to Macromolecule-Ligand Interactions", J. Mol. Biol., 161, pp 269-288 (1982)), it is available from University of California, San Francisco, CA.

B2

Please replace the paragraph beginning at line 12 of page 37 as shown. Applicants enclose a separate page indicating the amendments to the specification with deletions indicated by bracketing and additions indicated with underlining.

For example, the mutant may be screened on a change in charge at a physiological pH. This can be determined by the isoelectric point of the mutant RRF in comparison with the isoelectric point (pI) of the wild type parent. The isoelectric point can be measured by gel electrophoresis by the method of Wellner, D. et al., Ann. N.Y. Acad. Sci. 209: 34-43, 1973. The mutant in which surface charge has changed is an RRF polypeptide having a substituted amino

B3

B3 cont

acid positioned at a surface of the enzyme and a changed pI as provided by the structural data of the present invention.

Please replace the paragraph beginning at line 4 of page 53 as shown. Applicants enclose a separate page indicating the amendments to the specification with deletions indicated by bracketing and additions indicated with underlining.

Aminoglycosides such as streptomycin, paromomycin, and gentamycin are known to inhibit themselves from binding to the A site of the transfer RNA by binding to the A site of ribosome (Moazed, D. & Noller, H.F., Nature 327, 389-394 (1987); Fourmy, D., Yoshizawa, S. & Puglisi, J.D., J. Mol. Biol., 277, 333-345 (1998); Yoshizawa, S., Fourmy, D. & Puglisi, J.D., EMBO J., 17, 6437-6448 (1998)). Therefore, according to the model in Fig. 5, the above-

B4 mentioned aminoglycosides should inhibit the binding of RRF to the A site and if such a binding is inhibited, the dissociation process of termination complex due to the RRF should also be inhibited. Accordingly, whether the dissociation process of termination complex is inhibited or not in the presence of the above-mentioned aminoglycosides was examined by use of the amount of transfer RNA released from the ribosome and the amount of ribosome released from the messenger RNA as indices.

Remarks

Applicants have amended the specification to correct typographical errors. No new matter has been added.

Respectfully submitted,

John R. Van Amsterdam
Reg. No. 40,212
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210
Tel: (617) 720-3500

Attorney's Docket No.: K0448/7012
Date: March 6, 2002
xNDD